

REMARKS

Claims 1-20, 25 and 26 are pending in the application. Claims 25 and 26 have been canceled. Claims 1, 3, 5 and 14 have been amended. In view of the amendments, above, and the following remarks, Applicants respectfully request reconsideration and withdrawal of the rejections set forth in the above-identified Office Action.

Applicants note with appreciation the Examiner's statement that the presently pending claims are free of prior art, "because the cited prior art of record fails to teach or suggest a composition comprising bipotent hepatic progenitors which express at least one ICAM antigen and do not express MHC class 1a antigen, where the bipotent hepatic progenitors have the capacity to differentiate (claims 1-20)."

In fact, the present invention is directed to bipotent hepatic stem and progenitor cells having a unique phenotype, characterized as the presence of absence of certain cell surface markers, and methods of isolating such cells. Cells of the present invention are negative for the classical major histocompatibility complex (MHC) class Ia antigen, positive for intercellular adhesion molecule 1 (ICAM-1), and dull positive for nonclassical MHC Ib. Typically, characterization of the cell surface markers is performed by fluorescent immunostaining, whereby a strong (positive) signal is indicated by bright fluorescence and a negative signal is indicated by a lack of fluorescence. A dull positive signal, as defined in the specification on page 12, line 23 to page 13, line 4, and as is well known by those skilled in the art, is indicated by an intermediate level of

fluorescence (i.e., fluorescent signal is present, but the light intensity is not so bright as the amount of fluorescence generated by a full positive signal).

Claims 1-20, 25 and 26 were rejected under 35 USC 112 first paragraph for failure of enablement. Specifically, the Office Action states at pages 3 to 4 that "the specification does not reasonably provide enablement for methods of treating a liver disorder or dysfunction with liver progenitors in a subject in need thereof, ... or a method of treating a genetic disorder in an individual in need thereof comprising administration of an effective amount of a bipotent hepatic progenitor harboring a gene which corrects a genetic disorder." Applicants respectfully point out that only claims 25 and 26 are directed to these methods. Claims 1-20 are directed to compositions of hepatic progenitors, not methods. Therefore, the enablement argument made in the Office Action is not applicable to claims 1-20. In fact, the Office Action states with particularity at page 3 that the specification is "enabling for a composition comprising bipotent hepatic progenitors which express intercellular adhesion molecule-1 (ICAM-1) and do not express major histocompatibility complex (MHC) class 1a antigen, in which the bipotent hepatic progenitors have the capacity to differentiate into either hepatocytes or biliary cells in vitro, and the hepatic progenitors express a dull positive in fluorescence-activated cell sorting (FACS) for at least one MHC class 1b antigen." Therefore, Applicants respectfully request that the rejection to claims 1-20 be withdrawn and the claims be allowed.

With respect to claims 25 and 26, these claims are deleted without prejudice by this amendment. This amendment does not constitute an admission by Applicants with

regard to the arguments presented in the Office Action related to claims 25 and 26, and is made solely to further the prosecution of the present application and for the purpose of placing the present application in condition for allowance. Applicants reserve the right to claim the content of claims 25 and 26 in a divisional or continuation of the present application, or in another application. Inasmuch as deletion of claims 25 and 26 traverses the rejections to those claims, Applicants respectfully request the withdrawal of the rejections to those claims and allowance of the present application.

Claims 1 through 20 and 25 were rejected under 35 USC 112 second paragraph as being indefinite for failing to distinctly claim the subject matter which applicants regard as the invention, as indicated by the Office Action at pages 11-12. In particular, the Office Action noted typographical errors in claim 1, from which claims 2-13 depend, and unclear language in claims 3, 5, and 14 (from which claims 15-20 depend). Claim 25 is was rejected as incomplete.

Claim 1 is amended herein as recommended by the Examiner. Applicants believe claim 1 is now in condition for allowance and respectfully requests that the Examiner withdraw the rejection to claim 1 and allow claim 1 and the claims depending from it.

Claims 3 and 14 are amended to clarify the meaning of the term "weakly." As noted in the Office Action at page 6, the specification teaches that hepatic progenitors can be isolated by the dull expression (i.e., intermediate intensity of fluorescence during FACS) of MHC class 1b antigen. Applicants suggest that weak expression of the MHC class 1b antigen, as is well known in the art, may be clearly defined by the dull intensity,

exhibited in FACS, of fluorescence resulting from immunostaining of the MHC class 1b antigen on cells of the present invention. Claims 3 and 14 are amended to recite the clarifying language, "as indicated by a dull positive response to immunostaining with fluorescent anti-MHC class 1b antibody," following the term "weakly."

Claim 14 is also amended to clarify the meaning of the term "higher." Referring to figure 4C-1 of the present application, in particular the x-axis of that figure, one can see that sidescatter (SSC) is numerically assessed by FACS; in this case the value may be from 0 to 4095. One

SSC value may, therefore, be said to be "higher" or "less than" another SSC value in relation to its numerical score as determined by FACS. Claim 14 is amended to recite "a numerically higher sidescatter value determined by flow cytometry than the sidescatter value of non-parenchymal cells." Applicants suggest that this additional language makes the meaning of "higher" clear, and overcomes the rejection. Applicants respectfully suggest that this amendment, in conjunction with the amendment clarifying the term "weakly" as noted above, puts claim 14, and those claims depending from it, in a position of allowability. Applicants respectfully request that Examiner withdraw the rejections of claim 14, and claims 15-20 which depend from it, and allow those claims.

For the same reasons, amendment of claim 5 to recite, "a sidescatter value determined by flow cytometry which is numerically less than the sidescatter value of mature parenchymal cells" clarifies the meaning of "less than" in claim 5. Thus, Applicants respectfully suggest that this amendment puts claim 5 in a position for allowance. Applicants respectfully request that Examiner withdraw the rejections of

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claim 5 and allow the claim.

The Office Action rejects claim 25 as incomplete. Inasmuch as claim 25 is deleted by this amendment, this rejection has been rendered moot. Applicants respectfully request that the rejection be withdrawn and the remaining claims of this application be allowed.

For the above-noted reasons, the remaining pending claims are allowable over the cited art and are in condition for allowance. Applicants respectfully request that all rejections to the claims be withdrawn and the claims be allowed.

CONCLUSION

Applicants submit that the present application is in condition for allowance. Favorable reconsideration, withdrawal of the rejections and objections set forth in the above-noted Office Action, and an early Notice of Allowance are requested.

No additional fees are believed to be necessary. However, the Commissioner is authorized to charge any shortage in fees due in connection with the filing of this communication, or credit any overpayment, to Deposit Account No. 50-1710.

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Respectfully submitted,



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MARKED-UP VERSION OF CLAIMS
SHOWING CHANGES MADE

1. (Amended) A composition comprising bipotent hepatic progenitors which express at [At] least one intercellular adhesion molecule (ICAM) antigen and do not express major histocompatibility complex (MHC) class 1a antigen, in which the bipotent [bipoint] hepatic progenitors have a capacity to differentiate.

3. (Amended) The composition of claim 2 in which the MHC class 1b antigen is weakly expressed as indicated by a dull positive response to immunostaining with fluorescent anti-MHC class 1b antibody.

5. (Amended) The composition of claim 1 in which the hepatic progenitors have a sidescatter value determined by [in] flow cytometry which is numerically less than the sidescatter value of mature parenchymal cells.

14. (Amended) A composition comprising hepatic progenitors, their progeny, or a combination thereof in which the hepatic progenitors and their progeny:

(a) weakly express, as indicated by a dull positive response to immunostaining with fluorescent anti-MHC class 1b antibody, at least one MHC class 1b antigen;

(b) exhibit a numerically higher sidescatter value determined by [in] flow cytometry than the sidescatter value of non-parenchymal cells; and

(c) express alpha-fetoprotein, albumin, CK19, or a combination thereof.